REMARKS

I. Status of Claims

Claims 1- 4, 6-43 and 45 are cancelled.

Claims 5 and 44, 46-51 are being prosecuted.

Support for the new claims is found in the specification. For the pentapeptide library, there are 10 permutations for 3 aromatic residues per peptide, e.g., positions 1, 2 and 3, and 1, 2 and 4, etc; there are 5 permutations for 4 aromatic residues, e.g., 1, 2, 3 and 4, and 1, 2, 3 and 5; for 5 aromatics per peptide there is only 1 permutation, i.e., 1, 2, 3, 4 and 5 (all positions have an aromatic amino acid). Then, at each permutation and for each position, there are the 3 aromatics possible per position = 3 to the 3rd power. For the peptides having 3 aromatics, the other positions are either G or A, so the permutations at the other 2 positions is 2 to the 2nd power. So, the number of pentapeptides having 3 aromatics is 10 (permutations) x 3 to the 3rd power x 2 to the 2nd power = 1080 different peptide sequences containing the 3 aromatics. Those pentapeptides containing 4 aromatics calculates to 810 sequences; and those pentapeptides containing 5 aromatics calculates to 243; so the total containing 3 or more aromatics is = 2133; divide that number by the total possible pentapeptides (= to 5 to the 5th power, i.e., 5 positions with 5 possible amino acids at each of those positions = 3125; 2133 divided by 3125 = 0.68256 = 68.256%.

For the tetrapeptides either G or A not both can be used, so the calculation is 73%. For the hexa- and hepta-peptides, both G and A are used.

On page 4, para 0015, "..., about 30% or more of the D-peptides comprise three or more aromatic D-aromatic amino acids. Still more suitably, 40% or even as many 50% or more of the D-peptides comprise at least three or more aromatic D-amino acid residues;" and on page 5, para 0020; "Suitably, a D-peptide according to the present invention comprises a sequence of from three to seven D-amino acid residues in length, which sequence comprises at least two aromatic D-amino acid residues. More suitable, the sequences comprise at least three or four aromatic D-amino acid residues."

The solubility issue of the peptides is addressed as to the many solutions on page 9, para 0037; many examples are given.

Further support for the importance of three or more aromatic amino acids in binding to proteins is found on page 24, para 0075: "Of the total sequences obtained, 90% contain three or four

aromatic D-amino acids. Of those sequences identified from the G and A sublibraries (i.e., D-peptides with G or A residues at the amino-terminus), 89% contained three or four aromatic D-amino acids." Also support for three or more aromatic amino acids is seen with results of Table 7, page 25 and para 0081 showing that 92% of the peptides as identified as binding to TNF and TGF proteins contained three (22%), four (63%) or five (7%) aromatic amino acid residues.

II. Momany Does Not Teach the Claimed Elements

Claims 5, 44 and 46 were rejected as anticipated by Momany.

The examiner states that Momany teaches a family of peptides. A "family" is not a "combinatorial library."[1] To anticipate, all claim elements must be taught by the publication cited.

Also, Momany is missing the element of claim 1 "the remaining amino acids are selected from the group consisting of glycine and D-alanine" - therefore cannot anticipate.

The examiner proposes that since Momany teaches Gly at J3, this is equivalent to the pending claims. Momany described 20 groups of peptides (page 5), only two of which could be considered as pertinent to the pending claims. Group III can contain 3 D-aromatic residues. Additionally J3 has glycine as only 1 of 11 options. Claim 5 says D-alanine, which is not in these Momany groups. Momany has a D-alanine in positions J2 and J9 but these are not pertinent as neither of those positions are in groups III or XIII. Groups III and XIII are the only ones that contain 50% of peptides with 3 D-aromatics. Position J3 in group III is glycine or several other L-configuration amino acids and there is no D-alanine. In contrast, the positions of the A or G residues in the present libraries, as well as the aromatic amino acid residues, may be in any of the positions of the peptides.

Momany's synthetic peptides have pituitary growth hormone releasing activity. Those of skill in the art would not be directed to Momany to form a combinatorial library as is in claim 5 to find peptide structures containing aromatic amino acid residues to any other protein of interest.

The first 3 amino acid positions of group III consist of position number 1 (designated by Momany as Y3) which can be Tyr (any amino acid without configuration notation is of L-configuration), [Tyr, D-Tyr, Trp, D-Trp, Phe, or D-Phe], positions 2 and 3 are designated Z3 and E3

[1] A combinatorial library is a group of compounds that represent the various combinations of the elements of the library. Thus, for peptides a combinatorial library is all the possible combinations of the various amino acids defined to compose the elements of the library. Combinatorial peptide libraries were not known in 1980.

which both consist of D-Tyr, D-Trp or D-Phe; positions designated G3 and J3 can consist of several different amino acids, all of L-configuration, not D, including G3. J3 can consist of several different amino acids, all of L-configuration, including (G3) of lysine or arginine. Because positions 2 and 3 are all D-configuration Tyr, Trp or Phe, and position 1 can be either L- or D-configuration Tyr, Trp or Phe, necessarily all permutation of peptides in this Group III consist only of 50% of 3 aromatic amino acids of D-configuration (because position 1 contains one half of D- and one half of L-configuration aromatic amino acids). Thus...this does not teach claim 5 "at least 68% D-configuration aromatic amino acids."

In the present application, for example, a pentapeptide library consists of the elements (all D-configuration) of F, Y, W, A and the achiral residue glycine. Five amino acids permutated at 5 positions, yields a library of 3125 members, and of the total of 3125 penta-peptides, 68% will contain 3 or more D-configuration aromatic amino acids.

The peptide family claimed by Momany would consist of 6 x 3 x 3 x 2 x 11 (the numbers of amino acids possible at each position) members (defined by Momany at positions designated Y3 - Z3 - E2 - G3 - and J3) or a total of 1188 members (and 24,948 members considering the different amino and carboxyl-terminal functional groups used by Momany). Because the first amino acid position of Y3 consisted of either the D- or L-configurations of the aromatic amino acids Tyr, Trp or Phe, the total library of group III would be 50% of peptides containing the 3 aromatic amino acids of D-Tyr, D-Trp and D-Phe. This does not anticipate claim 5.

Momany related peptides which would be probed together for the growth hormone (GH) receptor but Momany synthesized only certain peptides. The number of peptides synthesized was 150, of which only 3 contained 3 D-configuration amino acids of Tyr, Trp or Phe. 3/150 is only 2% of the total. Thus, Momany does not approach, even close, claim 5 to a library consisting of at least 68% D-aromatic amino acid residues.

Momany used DMSO to dissolve the peptides and then added that solution to the biologic assay mix – he used DMSO, because it is likely he knew there were solubility issues.

Momany made the peptides described using standard protein synthesis methods which includes making the peptides on beads and then cleaving them off the beads. The examiner realizes there is no PEG linker (used by Momany in his syntheses) to effect solubility of peptides in water based buffers. In the present claim, the peptides remain on the support.

III. A Prima Facie Case of Obviousness is not Established

Not only are claims not anticipated, but adding Barany does not provide elements missing in Momany. As the examiner admits, Barany teaches only a polyethylene glycol linker to the beads as in claim 47. However, the reason for the use of the linker in the present claims is to enhance water solubility of peptides, not for the examiner's suggestion of motivation to provide "better quality peptides" (Office Action page 5).

"To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." MPEP § 706.02(j) *quoting Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). A determination of obviousness requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR International Co. v. Teleflex, Inc.*, -- U.S. --, 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007) *quoting Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

> the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR, 127 S.Ct. at 1740-41 (emphasis added). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741.

IV. Other issues

Applicant thanks the examiner for withdrawing previous rejections, and request allowance of the pending claims. Please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (45240-105719).

Respectfully submitted,

Alice O. Martin
Registration No. 35,601

Date: April 21, 2008
Barnes & Thornburg LLP
P. O. Box 2786
Chicago, IL 60690-2786

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